THE RISE OF SYNTHETIC DRUGS IN THE AMERICAN PHARMACEUTICAL INDUSTRY*

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The earliest concept of the use of drugs for the treatment of disease arose long before recorded history, but the search for synthetic chemical agents for this purpose began to assume its modern form only about a century ago. Yet, like the flowering of a plant, there was much quiet growth long before the first blooms appeared.

Man has always shrunk from the pain of illness and the terrors of death. His attempts to postpone the inevitable led to a groping search for something which would be helpful. Thus the very idea of a medicine was created—"born of need", Claude Bernard said. "From the first time anyone was ill, man went to his aid and sought to cure him with whatever came to hand. From its cradle medicine has therefore been applied science mixed with religion and with the feelings of sympathy that man experienced one for another." Primeval man found himself in a world hard to understand. In his search for explanations he ascribed diseases to supernatural visitations. Hence, it was logical that the priest should be the first "physician". His role was two-fold: to prevent the demons of darkness from possessing man and, failing in this, to drive out the evil spirits which had invaded the body. Medicine was witchcraft, white magic – locked like Ying and Yang in eternal conflict with the black arts. Its methods were largely religious; its therapy, mystical. In fact, the original meaning of the word "pharmacy" signified a form of witchcraft involving drugs to produce death.

There is a definite relationship between the concept of disease and the methods adopted to counter it. As long as the old idea held that disease was due to malign influence from without, magical methods of treatment were, without question, perfectly appropriate. With the con-

* Presented by Dr. Tainter as part of a symposium, *A History of the Drug House,* at the Thirty-first Annual Meeting of the American Association for the History of Medicine, held at The New York Academy of Medicine and at The Rockefeller Institute, New York, N. Y., May 22-24, 1958.

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cept that disease is a reaction of the body itself to changes in the external and internal environment, it was finally realized that rational therapeutics must take the form of aid to the natural defenses of the body. But, millenia were to pass from the incantation of a witch doctor to the deliberate, coordinated research which leads now to the discovery of new synthetic therapeutic agents.

At the beginning of recorded history man had become dissatisfied with fantasies as explanations for the perplexing questions of sickness and therapy, so in the Near East and Egypt the search that was to become medical science began over seven thousand years ago. There were no independent sciences of chemistry, biology or physics—it was only a single quest for knowledge. In the Nile Valley medicine had its first fine flowering. From the Ebers and other papyri we know that the Egyptians used many therapeutic agents which were, as they were to remain for ages, largely of plant origin. Botanicals were the mainstays of the physician-priest's armamentarium, augmented by some animal products and a few minerals. Around the temple courts a rudimentary chemistry developed in which a few inorganic chemicals were used. Indeed, sulfur, iron salts, magnesia, slaked lime, soda and nitre recorded in Egyptian medical manuscripts still appear in our present pharmacopeias.

The intense curiosity of the Greeks, who studied avidly every aspect of the living and non-living alike, advanced medicine through the time of Galen, about 200 A.D. During this period pharmacy and medicine were not separate entities but rather both were the province of the physician and his assistants, who gathered herbs and barks to prepare from them the decoctions used for treatment. Galen himself was renowned not only for his purely nosological studies, and as the founder of experimental physiology, but his developments in preparing plant extracts were so extensive that even today pharmacists refer to extracts of botanicals as "galenicals". In his period, following the principles of Hippocrates, diseases were looked upon as disturbances of the body and every effort was made to approach therapy rationally, rather than mystically.

With the fall of Rome, progress in Western Europe practically ceased for nearly 1000 years, but in Egypt and the Near East the ostracized Nestorian Christians continued to practice and teach in the Greco-Roman tradition. When the green standard of the Prophet swept westward out of Arabia, his followers carried medical knowledge beyond the Pillars of Hercules. While Europe was steeped in a newer mysticism—trying to drive out disease demons with amulets, religious exercises and saintly relics—Islamic medicine, leavened with the ferment of rational Hippocratic principles, dominated from Cordoba to Baghdad. As Moslem society matured, religious inhibitions unfortunately retarded progress in medicine proper but did not prevent the creation of hospitals and the development of pharmacy and alchemy. The practice of pharmacy became distinct from medicine. It was regulated and systematized in official books of formulae. In fact the first London Pharmacopeia was openly based largely on a Moslem formulary. The Arabs collected earlier Greek knowledge of chemistry and supplemented it with developments of their own. Medical training was rigorous and, even though anatomy and surgery were shunned for religious reasons, physicians were all schooled in chemistry. Indeed, many prominent Moslem physicians were also alchemists or pharmacists of note. At this time mercury, arsenic and the sulfates of copper and iron entered therapeutics.

From Spain via Salerno this knowledge seeped back into Western Europe with an influence that would remain long after Mohammedan political power had waned. Gradually this medical learning and its concepts of alchemy and pharmacy spread across Europe with increasing acceptance until the Holy Roman Emperor Frederick II in 1240 A.D. was moved to issue the first edict which regulated pharmacy as a profession for the collection, preparation, storing and selling of drugs.

In time, however, these fragments of Greco-Roman Arabic learning were shorn of their vitality and ossified into the medieval pattern of unassailable "authoritarian" doctrine. Ultimately the influence of new ideas undermined the rigid framework of Galenical logic and dogma. Then, when the fall of Constantinople brought a flood of original Greek manuscripts into Europe, the newly-invented printing press led to their widespread availability. Promptly a movement arose to return to the original precepts, and in the resulting ferment men became ready to believe what they saw and not what they read. Here and there, a few dared open revolt against "system", medieval or neo-Greek. With the flowering of the Renaissance, science once more pressed forward. In medicine Vesalius established anatomy on sound principles and William Harvey gave new life to physiology.

But from the view of our present topic, the most remarkable medical rebel of the Renaissance was the brash, egotistical Paracelsus, born in 1493. Son of an alchemy-minded physician and a former hospital superintendent, his inclination to the chemical side of medicine was to be expected. Three main principles consumed Paracelsus: a violent opposition to the ancient authorities, a disdain for the fantastic polypharmacy of his day, and a militant belief in chemical specifics for diseases. He was a bold experimenter in both the alchemical laboratory and the clinic. Through his efforts opium, mercury, lead, sulfur, iron, arsenic and copper sulfate were entered into the Pharmacopeias. He introduced mineral baths and popularized tinctures and alcoholic extracts. He urged the preparation and use of simple specific formulae for treatment. His own preparations, though glorified with such romantic names as catholicons and panaceas, were nonetheless for specific complaints. Many formulae ascribed to Paracelsus are as hopelessly complex as the traditional Mithridatums and Theriacs and, hence, at complete variance with his teachings, but there is reason to believe that these may not be accurate portrayals of his own remedies. His enemies and his preposterous boasting long prevented a just estimate of his accomplishments, but it now seems evident, when freed from the cloud of his unfortunate personality, that he enriched both medicine and chemistry and may truly be looked upon as the founder of chemotherapeutics.

Thus, by the mid-1500's the classic temple of scholastic medical tradition was collapsing, but the body of scientific knowledge was not yet adequate to replace it. Hence, speculative philosophy replaced authority. Finally in the 17th and 18th centuries man began to appreciate that nature operates in accordance with discoverable laws: first physics and, later, chemistry began to flower. Even though many of the physical laws were soon grasped, men of this age did not probe so deeply into the infinite complexity of life for, while physical experiment and philosophy were in mode, biological studies were still somewhat beneath the notice of a gentleman. However, lack of medical knowledge was no deterrent to the development of new approaches to therapeutics. Discoveries in the physical sciences were grafted into medicine to create schools of iatrophysics, iatrochemistry and iatromathematics. Where the simple physical laws did not quite fit living phenomena, gaps in knowledge were neatly plugged with ingenious logic. For nearly three centuries medicine continued to stumble about in blind empiricism, progressing largely by chance observations. During this period quacks enjoyed a heyday.

With the 19th century the stage was set for the attainment of Paracelsus' goal when chemistry would bring forth not gold but medicine. The infant American pharmaceutical chemical industry had already been launched by a firm of wholesale and retail druggists, the Marshalls in Philadelphia, who commenced the manufacture of sal ammoniac and Glauber's salt in 1786. However, progress was very slow through the first four decades of the century. True, Farr and Kunzi, a predecessor of Merck & Co., began manufacture of "pharmaceutical" chemicals at the time of the War of 1812, and the separation of the alkaloids from cinchona bark in France stimulated the production of quinine by a number of American firms in the 1820's. Still, raising and selling crude botanical drugs was the mainstay of the industry, which was dominated by the Shaker sect of Lebanon, New York, who gained world-wide fame for reliable, high quality medicinal herbs and extracts. The Tilden Company of New Lebanon was established in 1824 in this region and continues today as a respected manufacturer of ethical pharmaceuticals. Four years later, in the same year that Wohler synthesized urea, William S. Merrill opened the drug shop that was to become another honored member of American pharmaceutical industry. In this period an interesting innovation was the introduction of the sugar-coated pill.

Meanwhile, in Germany, under the stimulus of Liebig and his students, there was a tremendous upsurge in the synthesis of organic compounds following Wohler's demonstration that biologically important compounds could be made by synthetic chemical processes. In France a revolution in biological thinking and medicine itself was in the making. The vitalistic philosophies of Bichat were the fashion of the day. Life was looked upon as a mysterious supernatural phenomenon which acted arbitrarily and was largely independent of all physical laws relating to non-living phenomena. From the chemical side, Wohler's synthesis of urea was a severe blow to vitalism, but it was already tottering from the furious attacks of François Magendie and others, who firmly believed that physiological phenomena were entirely explainable in terms of physico-chemical laws. In attempting to avoid the pitfalls of the rigid scholastics and speculative philosophers before him, Magendie fell into many experimental errors of his own creation. Then Claude

Bernard became his assistant, and started the work which changed the entire course of scientific medicine and therapeutics.

Bernard was a unique combination of a profound intellect, a superb technician and a brilliant experimentalist. He perceived the deeper implications of Magendie's ideas which the older man himself had not appreciated, and transformed them into a complete philosophic concept of a new method for biological research. Through its application in laboratory animals, Bernard made fundamental discoveries that had broad application in clinical medicine ranging from treatment of carbon monoxide poisoning to safer, easier abdominal surgery. However, while his actual discoveries constituted major contributions to biology and medicine, they were not in themselves much more important than those of many others. It was the creation of the exquisite logical experimental method which led to those discoveries that made Bernard an intellectual giant of all ages.

In 1865 Bernard published his greatest contribution, a little book entitled, "An Introduction to the Study of Experimental Medicine". Here he gave in detail the reasons for his belief in the constancy of the internal environment, and codified the rules for experimental biological research. He showed, step by step, how these principles of logic were applied in making his own discoveries. Here was an agenda for future medical progress through controlled experimentation.

During the score of years which Bernard spent in perfecting his methods of experimental medicine other key elements essential to the eventual establishment of an American pharmaceutical industry were moving forward. In the 1840's the synthetic organic materials, ether and chloroform, were first employed for dental and surgical anesthesia. At this time the founding of two prominent companies in the pharmaceutical industry, Sharp & Dohme and Pfizer, took place, the first as a drugstore, the second as a bulk supplier of santonin. Important pharmaceutical industrial techniques adaptable to large scale manufacture rather than the prescription counter were beginning to appear. In 1843, when Bernard was announcing his first discoveries, Jacob Dunton began the manufacture of compressed tablets in Philadelphia, and through the 1850's and '60's the pace quickened on all fronts.

In 1856 while attempting to synthesize quinine young William Perkin in England accidentally discovered the first aniline dye, mauve. As Bernard's experimental method was to biology, so here was the opening which led to a true synthetic organic chemical industry through whose expanding skills the molecular complexities required for drugs could be overcome. In Germany and Switzerland the significance of Perkin's discovery was quickly grasped and firms like Ciba and Bayer were founded to manufacture aniline dyes. Impatient to expand its line, Ciba took a momentous step and began independent research for new dye products in its Swiss laboratories in the 1860's.

In this country, however, industrial efforts were centering on heavy chemicals. Primitive packaging and shipping facilities restricted chemical manufacture to operations serving limited geographic areas. These limitations in distribution imposed by non-scientific considerations could not be overcome, so that the industry remained largely decentralized with growth up to 1918 reflected by additional manufacturing plants rather than larger ones. The latter half of the 19th century brought far-reaching improvements in equipment for mixing, heating, cooling and efficient recovery of end products of chemical reactions. By 1880 crude oil stills were just getting into operation although with very primitive control of the processes. Yields and purity of products were quite unpredictable, but a trickle of chemical starting materials to supplement the coal tar derivatives became available for use in synthesis of new medicinals.

In the pharmaceutical companies, efforts centered mainly on the organization of "full line" and specialty firms to supply galenicals and inorganic drugs. In 1844 Carroll Dunham Smith was established to supply homeopathic medicines which previously had all been imported from Germany. Claude Bernard's publication on internal secretions prompted John Carnrick's experimentations with galenicals and endocrine specialties which led to the founding of Reed & Carnrick. In a similar vein the late 1850's saw the rise of the Chas. H. Phillips Chemical Company, which produced Milk of Magnesia, and the William R. Warner Company.

The perfecting of a better method for making and purifying ether by Dr. E. R. Squibb, an assistant surgeon in the Navy, led to such a demand that he opened a small production laboratory in 1858. A disastrous fire on Christmas Eve left Squibb horribly burned while trying to save valuable records. In spite of the destruction of both eyelids and the loss of a hand he re-established his company with the financial backing of doctors who appreciated the importance of ether that was free of toxic impurities and constant in potency. This reliable surgical ether was the foundation stone upon which the present diverse ethical firm of E. R. Squibb & Sons has been built.

During the years of the Civil War most existing pharmaceutical houses rapidly extended their line of products, but largely in botanical extracts together with a few alkaloid principles and the general anesthetics. This led to a pattern of distribution on a national rather than a local scale. It was not until three years after the war that a German named Bott established the Albany Aniline and Chemical Works, probably the first integrated industrial synthetic organic manufacturing operation in the United States.

During this period, Bernard's ideas on biological experimentation engaged the attention of Louis Pasteur, a practical-minded French professor of chemistry, who became an avowed disciple of the great physiologist. Pasteur was, by training and intent, a fine chemist who was diverted into biology by circumstances. A request for help from the father of a student turned his attention to the fermentation of beet sugar to alcohol. That was the demise of the brilliant young chemist but his reincarnation as a biologist. Pasteur knew next to nothing about fermentation, but he was pragmatic and was convinced that the experimental method of Bernard was the oracle that would answer any questions man put to it. He succeeded, he said, because "this marvelous experimental method . . . interrogates nature, forces it to reply and never ceases until the mind is fully satisfied." He applied Bernard's experimental principles with vigor, precision and—above all—with unbounded enthusiasm. In fact, so dramatic were his achievements that they have obscured the importance of the magnificent experimental tool which made them possible. From his studies of industrial and agricultural problems Pasteur formulated the germ theory of disease and developed the basic techniques for bacteriological experimentation. In so doing he buried forever the theories of spontaneous generation of bacteria.

As Bernard had removed various organs from animals to produce degenerative disease states which he could then study, so Pasteur succeeded in producing bacterial diseases experimentally in laboratory animals and then sought ways of curing the infections. These investigations led to the conquest of several infections, the most important to man being anthrax and rabies. In the end, Pasteur explained fermentation and putrefaction, made possible preservation of foods by "pasteurization", developed the first experimentally produced vaccines against infectious disease and, most important, elaborated the experimental techniques which made possible the application of Bernard's methods to infectious disorders. This ability to produce infections at will was the tool which ultimately provided the route to the present virtual conquest of infection.

While these fundamental developments were going on, present American pharmaceutical companies began to appear in increasing numbers. In 1855 Frederick Stearns & Co. was organized in Detroit and pioneered complete disclosure of the ingredients in the labelling of its products. Parke, Davis & Co., founded in 1875, stressed the marketing of preparations of standardized strength. In 1876, the year that Koch exemplified his postulates in his classic study of the anthrax bacillus, Col. Eli Lilly founded his pharmaceutical company, still identified with his name and family.

Eighty years of the momentous 19th century had passed when the renowned German pharmacologist, Schmiedeberg, published his "Foundation of Materia Medica." It is of interest to note that the bulk of substances included in his text book were botanicals or extracts of active natural principles. There were just a dozen synthetic chemicals reported: ether and chloroform as anesthetics; chloral and paraldehyde as hypnotics; amyl nitrite for cardiovascular action; four external or "internal" antiseptics, carbolic acid, pyrogallol, thymol and benzoic acid; pyrocatechin and hydroquinone as antipyretics; and the first of the coal tar synthetics, salicylic acid, as an antipyretic and antirheumatic. This was pathetically small progress, it would seem, for all the years since Paracelsus; and yet, only six years before this, in reviewing the 19th century progress in industrial chemistry, Prof. J. Lawrence Smith could point to the preparation only of alkaloids such as quinine and morphine, and chloroform, chloral and ether, as medicinal products coming from American industry.

The decade of the 1880's was probably the real beginning of the present age of therapeutics. Pasteur established the concept of germs as the cause of infection, which made antibacterial chemotherapy a theoretical possibility. However, he also developed preventative vaccination for rabies, and in so doing probably delayed to some extent concerted efforts toward synthetic chemotherapeutic attack on other infectious diseases. It was, however, a major advance in treatment and the foundation of the biologicals industry. Soon synthetic drugs began to appear in earnest: antipyrine, sulphonal, phenacetin, salol, acetanilid and many others followed in quick succession.

On the industrial side in this country the Hudson River Aniline & Color Co. was formed at Albany in 1881 and affiliated with Frederick Bayer in Germany from whom they received intermediates. Shortly thereafter in 1888 this German firm saw the value of many of the new medicinal chemicals being created from aniline and other coal tar derivatives and undertook their manufacture in Europe. In Switzerland, Ciba began similar operations.

Several fine chemical firms like Merck and the New York Quinine & Chemical Works were founded in the 1880's. However, in general, the U.S. pharmaceutical industry was not yet concerned with the new synthetics, but was immersed in problems of supplying botanicals of uniform potency and action. It was in 1888 that G. D. Searle, a Civil War veteran, whose wartime experiences had stimulated an interest in medicine, formed a company for this very purpose. The line was soon impressively extensive, but of definite galenical emphasis. Probably typical of the period, an early catalogue listed 400 fluid extracts, 150 elixirs, 100 syrups, 75 powdered extracts, 25 tinctures and 150 botanicals. Also in this year Dr. W. C. Abbott chose a different approach in an attempt to supply his profession with standardized drug extracts by commercial preparation of "active principle granules."

In this same decade Eli Lilly & Co. began the first tentative attempts at research, largely of a pharmaceutical and botanical nature. Progress was sufficient to lead to the establishment of a "Scientific Division" which was largely an analytical department, but the direct predecessor to the present true research division. Another innovation of the closing years of the century was the establishment in 1891 by a dentist, Ralph B. Waite, of the Anti-Dolor Company, now continued as the Cook-Waite Laboratories. This company offered commercially prepared dental local anesthetic solutions, first with cocaine and later with synthetics such as Novocain, which marked the founding of a new branch of the American pharmaceutical industry.

By and large, however, until the outbreak of World War I the supplying of synthetic drugs in the United States was left to foreign firms, largely German. So, likewise, was research in the field of chemotherapeutics. Not all of this was due to inertia and short-sightedness on the part of the American pharmaceutical industry. Many essential ancillary industries were still lacking or struggling through the difficulties of their own postpartum periods. Pfaudler introduced the glass-lined tank only in 1884. By-product coking, which was an essential process to the supply of raw materials for many synthetics, was carried out for the first time at Syracuse, New York, only in 1891. The first crude instruments for controlling temperature, pressure and time of chemical reactions to give desired products were just becoming available. Electro refining of metals for corrosion resistant steel and alloys required in synthetic production was first carried out in 1908, when apparatus for working at elevated pressures was just beginning to appear. Well into the 20th century dozens of deficiencies in raw materials and equipment continued to restrain serious attempts for domestic organic chemical manufacture.

In 1898 the Curies discovered radium, and three years later it was used for therapeutic purposes. This was the first of a new kind of radioactive medicines whose number would not begin to expand until Abbott entered the field on a large scale a half century later. Meanwhile, around the turn of the century continental firms like Bayer and Ciba were establishing biological laboratories in addition to their older chemical research facilities. Almost every year saw the introduction of one or more important synthetic chemicals for medicinal use: Pyramidon, aspirin, Veronal, Suprarenin and Novocain. Endocrines enjoyed their first modern use, while the etiology of vitamin deficiencies began to unfold as Eikmann discovered the cause of beri-beri.

Until 1910 practically all the synthetic drugs of real value, except for some topical antiseptics, were useful not because they attacked and eliminated the cause of disease but because they modified the discomfort which the patient experienced from the disorder. They were symptomatic remedies in that they reduced fever, alleviated pain or brought sleep to "knit the ravel'd sleeve of care". Then another long-hoped-for medical triumph was secured through Bernard's kind of experimental approach. The vision of chemical cures for infectious disease had tantalized man for centuries. Paracelsus first actively advocated the idea during the Renaissance, but with the flight of time it seemed to recede always farther from realization. By the 20th century scientists had concluded that human tissues were far more susceptible to the poisonous effects of disinfectants than were bacteria; hence, internal chemical sterilization was regarded as a will-o'-the-wisp and hopes were centered on the apparently more reasonable approach of specific sera and vaccines.

By the turn of the century, the necessary ingredients were at hand for the creation of synthetic drug therapy in infectious disease. Bernard had elaborated the principles of logic for experimental attack on the problem, while development of the synthetic dye industry made possible new approaches through organic chemistry. The last element required, a pertinacious faith in the attainability of a supposedly chimerical goal, was provided by a saturnine and obstinate pathologist, Paul Ehrlich. Once something caught his interest nothing moved him. He early became obsessed with techniques for staining pathological specimens. Neither impending academic failure nor the carping of his residency chief could turn "the little dye dabbler" from the laboratory. From his innumerable experiments he learned that different dyes had specific affinity for certain cells, living as well as dead. Somewhat later, while working with Koch, Ehrlich concluded that microbes injure only those cells for which they have a chemical affinity, and then developed his theories of induced immunity. From these discoveries he was convinced that chemotherapy was entirely practicable. He set out "by dint of continuous and persistent effort applied to numerous chemical variations to discover chemicals which inflict the greatest possible injury upon the parasite without at the same time injuring the organism they infect."

The causative organism for the dread African sleeping sickness had just been isolated and scientists at the Institut Pasteur in Paris had discovered how to produce the disease in mice. Ehrlich chose this for his studies, set up an infected mouse colony and began to investigate the effect of aniline dyes on the invading microorganisms. Systematically he altered the affinity and toxicity of the dyes by subtly modifying the chemical structures of those which showed even traces of therapeutic activity. First a red and then a blue dye promised success as they, almost miraculously, cured mice of one variety of the disease. But then, at the brink of apparent victory, there were revealed a number of discouraging complexities. While Trypan red and Trypan blue were repeatedly successful in mice, in rats, guinea pigs and dogs they were hopelessly inadequate. The enigma of internal disinfection was much more complex than had been supposed. Not only the relative sensitivity of host and parasite but the variations in susceptibility of the subvarieties of microorganisms, and species differences in the host, were all interconnected with the complexity of a Chinese puzzle. It was a sobering disillusionment, enough to blunt the ardor of the staunchest; but, possessed with a doggedness that was sometimes mistaken for stupidity, Ehrlich regrouped his personal and intellectual resources, preparing to plod ahead on a new course.

He never returned to this problem, however, because identification of the parasite which caused syphilis was announced. Its similarity to the organism of sleeping sickness, plus the terror inspired by this widespread disease, was a challenge Ehrlich could not resist. So, he turned to study syphilis, armed with the knowledge that Paracelsus had said arsenic was of value against it, and that the English had discovered an organic arsenical, which, though toxic, was useful in sleeping sickness. First, a very similar parasitic infection was produced in rats and mice; then the organic arsenic molecule was altered step by step. Finally, the 606th variation was successful. After months of careful study in animals, the first dozen patients received Salvarsan. Early doses were overgenerous and some sufferers died but the others were cured. While far from the perfectly harmless compound sought, Salvarsan was effective and stood as unassailable proof of the feasibility of systemic chemical treatment for infectious disease.

Meanwhile, a seemingly unimportant event to the U.S. pharmaceutical industry took place at Greenbush (now Rensselaer), New York. In 1903 the German firm, Bayer, bought out the Hudson River Aniline & Color Company and, while dye manufacture continued, began the manufacture of aspirin and phenacetin from imported intermediates. Henceforth, from this plant there was a steady flow of new key chemical drugs such as Novocain, the Salvarsans, Veronal, Luminal, Pyramidon, Salyrgan, etc., to all parts of the country.

Not until the turmoil of World War I disrupted receipt of all imported intermediates or finished bulk chemicals did the nation or the industry realize the inadequacy of its technical "know-how" to produce such goods from domestically available raw materials. Tragedies such as the plight of epileptics who had known freedom from their affliction while using German Luminal jarred the scientific community to frenzied efforts. In universities young chemical talent struggled with synthetic problems like the search for a feasible method of preparation for phenobarbital, which was carried out at the University of Chicago. Industry too was called upon by the government. Abbott Laboratories succeeded in overcoming the desperate need of the Army for procaine and barbital. From these determined efforts came the "home-grown" talent and industrial skill to produce the synthetics which had so quickly become an indispensable part of the medical armamentarium. The nation learned a bitter lesson which stimulated the development of a vigorous and expanding chemical and pharmaceutical industry.

Ehrlich had sought a more perfect fulfillment of his chemotherapeutic dream during the remaining years of his life, but his sudden death and the convulsions of World War I completely disrupted this research. When peace was restored, those in Europe who followed Ehrlich found themselves groping in his footsteps along a not yet fully understood experimental path. Thus, they deserted Bernard's principles and were doomed, like the pre-19th century biologists, to only meager success. A quarter century of labor yielded only partially successful medicaments for syphilis, a few rather indifferent anti-malarials and some imperfect drugs for African sleeping sickness—therapy which was not startlingly successful. These were protozoan diseases caused by complex parasites of the animal kingdom which were not the major destroyers of mankind. It was bacterial diseases which slashed gaping holes in the ranks of the living. Much smaller single-cell plant-like organisms caused the tuberculosis, pneumonia, peritonitis, septicemia, meningitis and puerperal fever that were dreaded by both physician and patient. Bewildered by the lack of success against this type of disease, men's enthusiasm for chemotherapy ebbed and in despair Salvarsan was sometimes branded a fluke, and Ehrlich an unsound visionary whose basic tenets led nowhere. So, one by one they turned away from chemotherapy to sera, vaccines and tissue extracts.

What was wrong? Many of these infections could have been duplicated in test animals so that experimental study was possible, yet no great progress was forthcoming. At that time most of the successful synthetic anti-infective drugs contained elements like arsenic which were known to be poisonous. But this only seemed to confirm Ehrlich's idea of specific microbe poisons innocuous to the host. Mistakenly, many of his successors approached the problem cart-end first by starting with toxic elements like arsenic, bismuth and mercury and trying to find forms in which these would be better tolerated by man than by microbe. They become so enamored of toxic elements that they lost sight of Ehrlich's earlier success with dyes and his alternate suggestion that interfering with bacterial metabolism might offer another path of attack. How simple it now seems. Plants are nourished in a manner different from man, and so it would appear logical to find a chemical innocuous to humans which would give microbes such "indigestion" they would starve to death. But instead of searching for new ideas, facts were fitted to the specific poison theory and it was actually held during the 1920's that bacteria, in contrast to the complex protozoa, as a primitive form of life were so adaptable to adverse environment that they could resist any toxic compound which human tissues could tolerate. Here was a paradox: the only hypothesis demonstrated to work was pronounced unworkable.

Progress on the industrial side, however, was phenomenal. At the outbreak of World War I American pharmaceutical producers were quite incapable of turning out the few synthetic drugs then in use. As late as 1917 the domestic dye industry was largely lacking in the equipment needed for organic syntheses on a commercial scale and metallurgists and equipment makers in this country had little experience in turning out the more complex apparatus which up till then had been entirely imported. Even so, full scale manufacture was out of the question without an adequate supply of basic chemicals from by-product coking and petroleum cracking. A good flow was not achieved until after hostilities had ceased and European supplies were once more available. Fortunately, this did not deter the synthetic industry for, having learned a bitter lesson from their inadequacies, they carried through wartime plans and trained personnel, expanded, and equipped plants fully capable of turning out the chemicals and synthetic drugs we now know were vital.

At this time most of the impetus in medicinal chemical research remained in Europe, and somehow, through all this era of doubt, the German chemical industry clung to the possibility of utilizing dyestuffs. Thus, about 1930 a young scientist, Gerhard Domagk, was given the assignment of finding a synthetic remedy for infections. Day after day Domagk turned his infected mice to every shade in the spectrum as he went through the dye samples which seemed to flow unendingly from the chemical storeroom shelves. Here and there, he noted a hint of activity; and then every conceivable chemical relative of the promising dye was tested from his shelves or synthesized in the chemistry laboratories. After more than two years of tedious elimination Domagk found a brilliant red dye which saved infected mice from certain death. Not long after, a bottle of dusky red tablets was sent to a clinic for trial in human infections. The first case was a little 10-month old baby dying from an overwhelming skin infection of staphylococci which had invaded the bloodstream. Three days later the baby was startlingly carmine-hued from the dye, but the infection was gone. Immediately thereafter, the drug was tried successfully in pneumonia, meningitis and a long list of other serious infections. Then, in 1935, these ruddy little tablets were dubbed "Prontosil" and announced to the world. Within a year chemists at the Institut Pasteur in Paris discovered that the active principle of this chemically complex dye was a simple, colorless well-known dyestuff intermediate now called sulfanilamide.

In spite of the excellent results reported in Europe, the long years of little progress after Ehrlich had ingrained a deep disbelief about the validity of any report of successful chemotherapy. In the United States, as in Great Britain, exhaustive confirmatory animal tests were followed by cautious and skeptical human trial. Then the dramatic cure of the President's son from a seemingly fatal infection made the sulfa drugs front-page news.

At last, chemists and biologists had found a guide-post in the wilderness that had been chemotherapy. From laboratories all over the United States, such as Merck, Sharp & Dohme, Lederle, Winthrop, Monsanto, and Squibb, and from Europe as well, innumerable "sulfas" came tumbling out to attack "strep" and "staph" infections – and pneumonia, meningitis, gonorrhea, mastoiditis, and peritonitis too. They did not poison with toxic elements like arsenic but quite literally starved the bacteria to death by interfering with their nutrition. Death from dozens of once fatal diseases became less common and man's life span spurted upward.

With the discovery of sulfa drugs and antibiotics and new biologicals, death rates from infection have tumbled almost to the vanishing point. Tuberculosis, once the "captain of death", killed 500 per 100,000 population in 1850. Now, largely due to a method of producing experimental tuberculosis in animals which permitted search for chemotherapeutic weapons against it, the United States mortality in 1955 was about 10 per 100,000 and the rate is dropping steadily each year. Similarly, in the

20 years between 1933 and 1953, surgical appendicitis deaths were reduced to one-tenth of the pre-sulfa numbers as a direct consequence of the use of drugs developed through experimental studies of infections.

Malaria, once a racking lifetime ague, now not only can be controlled but cured in a few days by synthetic drugs, some like atabrine and Aralen originally from Europe, others like Plaquenil, Camoquine and Primaquine from the wartime cooperative program, or continuing efforts such as those at Parke Davis and the Sterling-Winthrop Research Institute. The conquest of each disease has come as the result of our ability to reproduce the infection in experimental animals and, therefore, to study the action of chemicals on it under controlled conditions according to Bernard's and Koch's precepts.

In the last quarter century improved synthetic drugs for the cure of infection, palliation of symptoms, and surer x-ray or laboratory diagnosis have come pouring out from the American pharmaceutical industry. With the advent of World War II, and the tremendous therapeutic advances sparked by our industrial research, the flow of new drugs from Europe to our nation has largely reversed, and now the world looks to us for the new synthetic remedies that will preserve life and, increasingly, make it worth living.

This has been accompanied by a tremendous expansion in the volume of use of pharmaceuticals. In 1939 the total drug sales, at manufacturers' price levels, was 301 million dollars. Eighteen years later in 1957 it had jumped to 2102 million dollars, a seven-fold increase. During this period, sales of the proprietary drugs advertised directly to the lay public went from 152 million to 425 million dollars, an increase of 2.8 times. But in contrast, the drugs used solely by physicians, the so-called ethical drugs, jumped from 149 million to 1677 million dollars, an increase of 11.3 times. It can be seen that the great increase has been in the potent specific drugs which require professional supervision to use.

Such volume of production could not have been achieved without tremendous expansion of the pharmaceutical industry. All through the 1930's a multitude of automatically controlled synthetic operations were introduced. New or improved control instruments kept untiring watch on the innumerable conditions which governed the synthesis of increasingly complex chemical drugs. From better temperature gauges to photoelectric eyes, electronic controls and spectrographic analysis, every device to improve quality has been utilized. The newest high strength corrosion resistant alloys permit much larger and more efficient equipment, especially for reactions carried out at high pressures. This has been accompanied by a steadily increasing quality of production, and a continuously decreasing cost of the drugs. Today the drugs required to cure an illness cost less than ever before, even though hospital costs and other ancillary expenses seem to have skyrocketed. Thus, the national average total expenditure for drugs in 1957 was only about $12.00 per person, while three times this amount was spent on tobacco and over four times as much on alcoholic beverages.

But the greatest saving in costs of medical care has not been in the price of the medicine, but in the reduction of duration of illness and losses through sickness and death. As our new chemical bullets become more potent and specific they are virtually eliminating one after another of the hitherto important causes of disability and death. The pharmaceutical industry can take justifiable pride in its share of this contribution to national welfare.

Projection of the present rates of increase in life span indicates that we may look forward to an average length of life of about 100 years by the end of this century. However, there will be no zest in life at 100 or 150 years of age if the mind is misty, eyes and ears untrue, the bones too brittle and one's digestion awry. As we subdue each former source of disability, control of the remaining diseases becomes more urgent. Thus, a whole new division of medicine, geriatrics, is being created to deal with the special problems of the aged. The development of worn-out organs and flagging minds must be prevented by new therapeutic discoveries. Too new to have made many major advances, geriatric medicine is attracting increased and vigorous attention in the American pharmaceutical industry, and will play an ever-widening role as we move toward the 21st century.

In retrospect, the whole process which is making life so much longer and more livable began a century ago when chemists, like Liebig, began to probe the potentialities of organic chemistry and Claude Bernard developed the concepts and methods essential to the systematic application of experimental reasoning to biological research. Through these techniques Pasteur, Koch and Ehrlich set in motion unparalleled progress in medicine and therapeutics by use of both the methods and fruits of chemical synthesis. Yet all of this would have been of but limited effect had not the simultaneous development of a responsible, competent pharmaceutical industry made available these new synthetic medicines in large quantity, high quality, and at steadily decreasing cost to vast segments of the world's population. Only the extensive experience and mass production of techniques of the pharmaceutical companies could have brought these wonder-working chemical bullets within the present reach of every man.

A highly skilled synthetic pharmaceutical industry has replaced the drug store back room of a century ago as the helpmate of the physician in the endless struggle against suffering and death. Through the years this industry has grown not only in ability and facilities but in responsibility to mankind through the profession it serves. Hundreds of thousands of men and women in its employ are devoted to the search for new and better ways to meet the challenge of present medical problems. There is every promise of continuing success. With each will come profound changes and new problems to be met in the spirit of Paracelsus, of Claude Bernard and of Paul Ehrlich.
